DOCKET NO. 9491-033-27

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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11/25/02

IN RE APPLICATION OF: BRIAN M. FENDLY, ET AL. ART UNIT: 1645
SERIAL NO.: 08/948,149 EXAMINER: SWARTZ, R.
FILING DATE: OCTOBER 9, 1997
FOR: ANTI-ERBB2 ANTIBODIES

RESPONSE

ASSISTANT COMMISSIONER FOR PATENTS
WASHINGTON, D.C. 20231

SIR:

This Response is submitted in answer to the Office Action dated July 16, 2002, which set a three month period for response. A Request for Extension of Time for one month is attached hereto and incorporated herein by reference, thereby extending the date for response from October 16, 2002 to November 18, 2002 (November 16, 2002 being a Saturday and November 17, 2002 being a Sunday).

REMARKS

Reconsideration and allowance of the above referenced application is respectfully requested. Applicants' earlier submitted arguments remain valid and are included with additional arguments in support of patentability of the claims.

Claims 28-40 and 42-62 are currently pending in the application.

Claims 28-31, 37-38, 40, 56 and 57 are rejected under 35 U.S.C. §102(b) as anticipated by or, in the alternative, under 35 U.S.C. §103(a) as obvious over Shepard et al.

(*J. Clin. Immunol.*, 11(3):117-127, 1991). Applicants respectfully traverse this rejection.

As earlier argued, the Shepard reference not only fails to anticipate the present invention but actually teaches away from Applicants surprising discovery.

The presently claimed invention is directed to methods for **inducing cell death** by exposing a cell that overexpresses ErbB2 to an isolated antibody that binds to the epitope on ErbB2 to which antibody 7C2 or 7F3 binds (i.e., to Domain 1 of ErbB2) (Claims 28-40 and 42-57 and 59-62) and a method for inducing cell death by exposing a cell that overexpresses ErbB2 to a first antibody that binds to the epitope on ErbB2 to which antibody 7C2 or 7F3 binds (i.e., Domain 1 of ErbB2) and subsequently exposing the cell to a second antibody that does not bind to the binding site of antibody 7C2 or 7F3 (Claim 58).

In maintaining this rejection, the Examiner, in discussing the Shepard reference at page 3 on the last line of paragraph 4, contends that "the claimed antibodies also exhibit the required activity." This statement is inaccurate.

While Shepard discusses the claimed antibodies in as being less active in "inhibition of proliferation" and in actually stimulating proliferation of several of the tumor cell lines, it absolutely **does not** teach a method for "inducing cell death" as claimed by the Applicants. Therefore, on its face, Shepard not only fails to anticipate the invention as claimed but actually teaches away from Applicants discovery. Shepard teaches the derivation of a family of monoclonal antibodies focused against the extracellular domain of $p185^{HER2}$. (See page 119, left column, lines 16-18). The monoclonal antibodies 4D5, 7C2, and 7F3 are some of these antibodies. (See Table I at page 122). Shepard teaches that these monoclonal antibodies vary in their ability to inhibit proliferation of breast tumor cells. "Inhibition of

proliferation" is not equivalent to a teaching of "inducing cell death." As mentioned above, Shepard clearly teaches that 7C2 and 6E9 are consistently less active than the other antibodies in inhibiting proliferation. (See page 120, left column, lines 19-21) and, further discloses that 7C2 has the ability to stimulate the proliferation of several of the tumor cell lines shown in Table III. (See page 120, right column, lines 4-8). Additionally, when these antibodies were compared for efficacy, as measured by their abilities to inhibit growth of breast and ovarian tumor cells overexpressing $p185^{HER2}$, muAb 4D5 was generally the most potent and was considered "a good candidate for further characterization." (See page 121, left column, lines 6-9). Considering the above discussed negative teaching of Shepard regarding the antibodies of the current invention, Shepard can hardly be considered a teaching that anticipates the Applicants' invention of a method of "inducing cell death" as currently claimed.

Based on these disclosures in Shepard, Applicants submit that one of ordinary skill in the art, if seeking to "inhibit proliferation," much less "induce cell death", would not have been motivated to experiment with 7C2 or with antibodies that bind to the same epitope as 7C2 (or 7F3). Further, any experiments of that nature that resulted in these antibodies inducing the death of an ErbB2 cell such as by apoptosis would have come as a surprise to the skilled artisan who relied on the teaching of Shepard. Because Shepard teaches away from the present invention, there would be no motivation to try and certainly no teaching of a likelihood of success for the skilled artisan to arrive at the Applicant's surprising discovery. Thus, not only does the teaching of Shepard fail to provide a reference which anticipates the claimed invention, it also fails to provide a reference which would provide a motivation to combine with other references or a teaching of a likelihood of success if combined with

another reference. For that reason Shepard would fail the test of a valid reference in an obvious rejection of the current claims. Without motivation, there cannot be a case of obviousness. Without a teaching of a likelihood of success there is not obviousness. "The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on the applicants disclosure." See MPEP 706.02(j) quoting In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

First, as set forth above, Shepard teaches that 7C2 is consistently less active in inhibiting the proliferation of breast tumor cells than the other antibodies shown in Table I and thus teaches away from the claimed invention. One of skill in the art reading this disclosure in Shepard would be motivated to experiment with an antibody other than 7C2 in experiments in which the inhibition or death of cancerous or tumor cells is desired (e.g., a cell which overexpresses ErbB2 as in the present invention).

Second, Shepard discloses that 7C2 actually stimulates the proliferation of certain types of cancers. This is the opposite of the presently claimed invention which induces the death of a cell which overexpresses ErbB2 (e.g., a cancer cell). As a result, one of skill in the art would not be motivated to experiment with 7C2, or antibodies that bind to the epitope that 7C2 binds and arrive at the present invention.

Finally, the disclosure set forth in Shepard that states that muAb 4D5 is the most potent of the $p185^{HER2}$ antibodies set forth in Table I against breast and ovarian tumor cells and is the best candidate for further characterization would certainly motivate one of skill in the art to experiment with 4D5, and not 7C2 or 7F3, or antibodies that bind to the epitope to which 7C2 or 7F3 bind.

In sum, Applicants submit that a disclosure of growth inhibition does not teach or suggest the inducement of cell death as presently claimed. Growth inhibition of cells can occur without cell death occurring. Thus, one of skill in the art would not arrive at the presently claimed invention based on the disclosure of Shepard.

Additionally, Applicants respectfully disagree with the Examiner's assertion in an earlier Office Action that the claimed properties of binding to the epitope to which 7C2 or 7F3 bind (i.e., Domain 1 of ErbB2) and 5-50 fold induction of annexin binding are inherent properties of the antibodies 7C2, 7F3, and 4D5 disclosed in Shepard. As discussed above, Shepard teaches the derivation of a family of monoclonal antibodies focused against the extracellular domain of $p185^{HER2}$. (See page 119, left column, lines 16-18). Of these monoclonal antibodies, some were shown to be growth inhibitory, some had no affect on breast or ovarian tumor cell proliferation, and some stimulated the proliferation of breast tumor cells. (See page 120, left column, lines 8-11). Because these monoclonal antibodies were all focused on the extracellular domain of $p185^{HER2}$ and possessed properties that were not always consistent with each other, it cannot be said that all antibodies that bind to the same epitope that 7C2 or 7F3 binds will necessarily have the same properties. Thus, Applicants again submit that Shepard does not teach or suggest methods for inducing cell death by exposing a cell that overexpresses ErbB2 to an isolated antibody that binds to the epitope on ErbB2 to which antibody 7C2 or 7F3 binds as is presently claimed.

Furthermore, Applicants submit that a statement that the properties of antibodies 7C2, 7F3, and 4D5 inherently have the same properties, without more, is insufficient to draw a conclusion that all antibodies that bind to Domain 1, or even to the epitope on Domain 1

where 7C2 and 7F3 bind, will necessarily have the same characteristics (e.g., induce cell death). For example, classes of antibodies exist in which antibodies have the same binding domain but behave very differently because they have different constant domains. IgG is but one example. Further, although antibodies may be able to bind to the same epitope, binding to that epitope may be conformationally dependent. In other words, binding of a particular antibody to a particular epitope may only occur when a particular region is located next to it, or only if that particular region is folded in a particular manner. The folding of the adjacent region could sterically hinder the binding of antigens to the antibody bound to the epitope, and thus may effect certain characteristics of that antibody (e.g., ability to induce death of a cell).

Additionally, although antibodies 7F3 and 7C2 are mentioned in Shepard (see Figure 2 on page 120), the reference does not enable these particular antibodies. In particular, antibodies 7F3 and 7C2 were not deposited with respect to the reference and their sequences were not disclosed in the reference in such a way that a skilled person could have reproduced those particular antibodies based on the reference. The antibodies 7F3 and 7C2 were not publically distributed or publically available more than one year prior to October 18, 1996, the effective filing date of this application.

As discussed in a previous response to an Examiner's Office Action, if an outside investigator had requested samples of the 7F3 or 7C2 antibodies prior to October 17, 1996, Genentech would only have provided the antibodies to the investigator if Genentech was able to approve a research plan proposed by the outside investigator. If the research plan was approved, Genentech would only have provided the research material to the outside

investigator under a Material Transfer Agreement (MTA). The standard Genentech MTA at that time imposed restrictions or limitations on the use of the research material. In particular, the laboratory receiving the research material under a Genentech MTA could only use the research material for a research plan approved by Genentech and could not transfer the research material to others outside the laboratory receiving the research material. The MTA further required that the outside investigator not disclose (orally or in writing) the results of the research until Genentech had been given time to review the disclosure and make recommendations or comment upon it. Thus, 7F3 and 7C2 were not publicly available and the cited reference does not qualify as prior art.

According to the MPEP, p. 2404.01:

> ...biological material is accessible because it is known and readily available to the public. The concepts of "known and readily available" are considered to reflect a level of public accessibility to a necessary component of an invention disclosure that is consistent with an ability to make and use the invention. To avoid the need for a deposit on this basis, the biological material must be both known and readily available - neither concept alone is sufficient.

Further, the MPEP (*id.*), in discussing the ready availability of biological materials states that biological materials that have restricted access due to "some requirement of law or regulation" ... "under conditions imposed for health, safety, or similar public interest concerns will be considered readily available"; however, this is true only "where the restrictions are imposed for the public, as opposed to the private, welfare." In the present case, Shepard does not provide an adequate disclosure of the claimed antibodies, no deposit of the antibodies was made, and access to the antibodies was very tightly restricted for the "private" welfare of Genentech. As indicated above, if access to the claimed material was granted for research

purposes only under a Genentech MTA, Genentech would have maintained the strictest control over the access and experimental use of the materials. Further publication was prohibited and the public accessibility to the materials was severely restricted for "private" not public welfare reasons. Thus, as discussed in the MPEP (*id.*) and prevailing case law cited therein, the materials were not readily available.

In view of the above, Applicants submit that the present invention is neither anticipated by, nor obvious over, Shepard and respectfully request that these rejections be reconsidered and withdrawn.

Claims 28-31, 37-38 and 40 are rejected under 35 U.S.C. §102(b) as anticipated by or, in the alternative, under 35 U.S.C. § 103(a) as obvious over Lewis et al. (*Cancer Immunol.*, 37:255-263, 1993). Applicants respectfully traverse this rejection.

Applicants respectfully submit that Lewis does not teach or suggest the present invention. In particular, Lewis does not disclose methods for inducing cell death by exposing a cell that overexpresses ErbB2 to an isolated antibody that binds to the epitope on ErbB2 to which antibody 7C2 or 7F3 binds (i.e., to Domain 1 of ErbB2) (Claims 28-40 and 42-57) or a method for inducing cell death by exposing a cell that overexpresses ErbB2 to a first antibody that binds to the epitope on ErbB2 to which antibody 7C2 or 7F3 binds (i.e., Domain 1 of ErbB2) and subsequently exposing the cell to a second antibody that does not bind to the binding site of antibody 7C2 or 7F3 (Claim 58).

Although Lewis discloses antibodies 7C2 and 7F3 in passing, Lewis does not teach or suggest the presently claimed invention, i.e., methods for inducing cell death by exposing a cell that overexpresses ErbB2 to an antibody that binds to the epitope on ErbB2 to which

antibody 7C2 or 7F3 binds. As set forth above, a statement that antibodies that bind to the same epitope inherently have the same properties, without more, is insufficient to draw a conclusion that all antibodies that bind to Domain 1, or even to the epitope on Domain 1 where 7C2 and 7F3 bind, will necessarily have the same characteristics (e.g., induce cell death). For example, classes of antibodies exist in which antibodies have the same binding domain but behave very differently because they have different constant domains. IgG is but one example. In addition, although antibodies may be able to bind to the same epitope, binding to that epitope may be conformationally dependent. In other words, binding of a particular antibody to a particular epitope may only occur when a particular region is located next to it, or only if that particular region is folded in a particular manner. The folding of the adjacent region could sterically hinder the binding of antigens to the antibody bound to the epitope, and thus may effect certain characteristics of that antibody (e.g., ability to induce death of a cell).

Further, there is no disclosure present in Lewis to motivate one of skill in the art to experiment with 7C2 or with antibodies that bind to the same epitope as 7C2 (or 7F3) and discover that these antibodies induce the death of an ErbB2 cell as claimed in the present application. As discussed above with regard to the Shepard reference, without a motivation to combine and a teaching of a likelihood of success of the combination from within the cited references themselves, there cannot be a case of obviousness.

For example, the results in Lewis suggest that antibody 4D5 is the most potent of the growth-inhibitory antibody and has the most consistent growth-inhibitory activity towards breast tumor cell lines. (See Lewis, p. 256, left column, lines 45-48 and p. 259, right column,

lines 1-3). In particular, Lewis notes that 4D5 had superior growth inhibition of SK-BR-3 (i.e., breast cancer cell). However, a disclosure of "growth inhibition" of cells does not teach or suggest the inducement of "cell death" as presently claimed. Thus, one of skill in the art would not arrive at the presently claimed invention based on the disclosure of Lewis. Further, Applicants submit that the disclosures set forth in Lewis would motivate one of skill in the art to experiment with 4D5, and not 7C2 or 7F3, or antibodies that bind to the epitope to which 7C2 or 7F3 bind, and arrive at the present invention (i.e., methods for inducing cell death by exposing a cell that overexpresses ErbB2 to an antibody that binds to the epitope to which 7C2 or 7F3 bind). The cumulative teaching of the cited prior art, including Shepard, would have had the opposite effect of motivation toward the present invention. One of ordinary skill in the art would have considered the present invention to be an impossibility. The cited references actually lead one of skill in the art away from the presently claimed invention, i.e., they teach away from the present invention.

Although antibodies 7F3 and 7C2 are mentioned in Lewis, the reference does not enable these particular antibodies. In particular, antibodies 7F3 and 7C2 were not deposited with respect to the reference and their sequences were not disclosed in the reference in such a way that a skilled person could have reproduced those particular antibodies based on the references. The antibodies 7F3 and 7C2 were not publically distributed or publically available more than one year prior to, October 18, 1996, the elective filing date of this application. If an outside investigator had requested samples of the 7F3 or 7C2 antibodies prior to October 17, 1996, Genentech would only have provided the antibodies to the investigator if Genentech was able to approve a research plan proposed by the outside

investigator. If the research plan was approved, Genentech would only have provided the research material to the outside investigator under a Material Transfer Agreement (MTA). The standard Genentech MTA at that time imposed restrictions or limitations on the use of the research material. In particular, the laboratory receiving the research material under a Genentech MTA could only use the research material for a research plan approved by Genentech and could not transfer the research material to others outside the laboratory receiving the research material. The MTA further required that the outside investigator not disclose (orally or in writing) the results of the research until Genentech had been given time to review the disclosure and make recommendations or comment upon it. Thus, 7F3 and 7C2 were not publicly available and the cited reference does not qualify as prior art. Further, as discussed above in regard to Shepard, Genentech established very tight restrictions on accessibility for research purposes only to the claimed materials. Thus, even if access to the materials was granted under a Genentech MTA, the access would have been severely restricted and controlled for the private welfare of Genentech and thus would not have been considered readily available under the MPEP and prevailing case law cited therein.

In view of the above, Applicants submit that the presently claimed invention is not anticipated by, or obvious over, Lewis and respectfully request that the Examiner reconsider and withdraw these rejections.

Claims 32-36, 39 and 58 are rejected under 35 U.S.C. §103(a) as being unpatentable over Shepard et al. (*J. Clin. Immunol.*, 11(3):117-127, 1991) or Lewis et al. (*Cancer Immunol. Immunother.*, 37:255-263, 1993) in view of Fendly et al. (*Cancer Research*, 50: 1550-1558, 1990), Deshane et al. (*J. Invest. Med.*, 43(Suppl 2):328A, 1995), and further in

view of Senter et al. (U.S. Pat. No. 4,975,278). Applicants respectfully traverse this rejection; the supporting argument is discussed below with the traversal of the rejection of Claims 42-55 and 59-62.

Claims 42-55 and 59-62 are rejected under 35 U.S.C. §103(a) as being unpatentable over Shepard et al. (*J. Clin. Immunol.*, 11(3):117-127, 1991) in view of Lewis et al. (*Cancer Immunol. Immunother.*, 37:255-263, 1993) in view of Fendly et al. (*Cancer Research*, 50: 1550-1558, 1990) and further in view of Deshane et al. (*J. Invest. Med.*, 43(Suppl 2):328A, 1995), and Senter et al. (U.S. Pat. No. 4,975,278). Applicants respectfully traverse this rejection.

As set forth above, the presently claimed invention is not taught or suggested by either Shepard or Lewis. All arguments presented above with regard to Shepard and Lewis are equally applicable to the rejections of the claims cited immediately above.

It is submitted that the teachings of Fendly, Deshane, and Senter do not make up for the deficiencies of Shepard or Lewis. Thus, Applicants submit that the combination of the Examiner's cited references neither teaches nor suggest the present invention. Further, Applicants submit that the negative teachings of Shepard and Lewis foreclose any possibility of a motivation to combine and a likelihood of success for the combination of the references, which if combine would still not result in the presently claimed invention. Thus, the present invention is not obvious.

In view of the above, Applicants submit that the present invention is patentable over Shepard et al. or Lewis et al. in view of Fendly et al., Deshane et al., and further in view of Senter et al. and is also patentable over Shepard et al. in view of Lewis et al. and Fendly et al.

and further in view of Deshane et al. and Senter et al. Accordingly, Applicants respectfully request that these rejections be reconsidered and withdrawn.

CONCLUSION

In light of the above, Applicants believe that this application is now in condition for allowance and therefore requests favorable consideration.

If any points remain in issue which the Examiner feels may be best resolved through a personal or telephonic interview, the Examiner is respectfully requested to contact the undersigned at the telephone number listed below.

Respectfully submitted,

PIPER RUDNICK LLP

March 18, 2002
Date

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